

REMARKS

This is a response to the rejections set forth in the Office Action mailed March 3, 2003.

Statement of Related Application

Applicant draws the Examiner's attention to pending application Serial No. 09/564,288 filed on May 4, 2000. The application is entitled TREATMENT OF AUTOIMMUNE DISEASES and is being examined by Examiner Ronald B. Schwadron.

Information Disclosure Statement

The Examiner notes in the Office Action dated March 3, 2003, that certain references cited in an Information Disclosure Statement, and provided to the Office, have not been received by the Examiner. Applicant has arranged for the hand-delivery of said references, pursuant to the suggestion of the Examiner, and respectfully requests that the Examiner consider the references, and provide an appropriate indication in the file wrapper that such references have been fully considered.

35 U.S.C. §112 Rejections

The Examiner has rejected amended claims 1, 5-16, 22 and 28 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For the reasons set forth below, Applicants respectfully traverse this rejection and request its withdrawal.

The Examiner has set forth several observations regarding the claimed invention, the disclosure and the perceived state of the art. Certain of these observations appear to suggest

that the invention, as claimed, will not work, while others appear directed to the knowledge and capabilities of a person of ordinary skill in the field of the invention relative to the claimed invention. The two types of observations implicate distinct potential grounds for the Examiner's conclusions that the claims are not enabled; namely, (i) that the invention lacks a credible utility, and (ii) that a person of ordinary skill would have to engage in undue experimentation in order to practice the invention as claimed. Each of these grounds will be addressed in turn.

(i) Credible Utility-Related Grounds

Several observations set forth in the last Office Action suggest that the Examiner believes that Applicants have not established a credible utility for the claimed invention (e.g., that the claimed method, when practiced, will not yield the specified results), and that on this basis, a rejection under 35 U.S.C. 112, first paragraph, is appropriate. In particular:

- At page 5 of the Office Action, the Examiner maintains that as of the effective filing date, the use of rituximab or any other anti-CD20 antibody *in vivo* applications (e.g. graft transplantation or for treating graft-versus-host or host-versus-graft disease) was still very limited and further investigation was required. The Examiner relies on a passage in Friend et al., that states "Monoclonal antibodies have proved to be of immense importance from a diagnostic and investigative standpoint. However in clinical transplantation their impact on therapeutic regimens have been rather disappointing." (page 1625, col.1, first paragraph).
- Also at page 5 of the Office Action, the Examiner states that "there is no evidence of record indicating or suggesting that the use of rituximab or any other anti-CD20 antibody would be effective in reducing or preventing the host humoral and/or T cell-mediated immune responses against a graft or for treating any graft-versus-host or host-versus-graft disease in a mammal to an extent that the graft would be survived and maintained for a sufficient period of time to yield any beneficial use."
- At page 6 of the Office Action, the Examiner continues that "... it is noted that rituximab has no effect on the total mean serum IgG and IgA levels of patients treated with the humanized monoclonal antibody", citing Leget et al., and Levine et al.). The Examiner further states, citing Wilkes et al., that "the

production of IgG2 antibodies plays an important role in human lung allograft rejection.” The Examiner then states that “it is unclear how the persistence of unaffected serum IgG and IgA levels in patients already treated with rituximab, and the ability of the treated patients to elicit an immune response against rituximab would not result in any adverse host immune response to a graft, so that the therapeutic and prophylactic effects contemplated by Applicants could be attained in the methods as claimed.”

- At page 8, the Examiner asks “in a mammal not suffering from a malignancy or in a mammal suffering from a graft-versus-host or host-versus-graft disease, would any anti-CD20 mouse monoclonal antibody, including the chimeric anti-CD20 monoclonal antibody rituximab, not be neutralized or destroyed by a treated mammal prior to any contemplated therapeutic effects would contemplated by the Applicants could be achieved? And how any mouse monoclonal antibody that lacks human effector functionality as noted by Anderson et al., would alleviate or prevent an immune response to a graft or treating a graft-versus-host or host-versus-graft disease in a human as encompassed by the instant claims?”

At pages 9 to 11 of the last Office Action, the Examiner responds to previous observations of the Applicants made in relation to the specification, the teachings of *Friend et al.*, *Wilkes et al.*, and *Leget et al.* The responses of the Examiner to these previous observations suggest that the Examiner believes the three disclosures identify specific challenges in the treatment of undesired immune responses to a graft, both in a normal mammal and in a mammal that is suffering from a malignancy that would call into question whether the claimed invention would yield the desired results.

Applicants respectfully invite the Examiner to consider evidence in the published literature subsequent to the filing date of the present application that shows the successful use of rituximab in blocking an immune response to a graft in a mammal not suffering from a malignancy according to the teachings of the present application.

For example, *Aranda et al.*, “Anti-CD20 Monoclonal Antibody (Rituximab) Therapy For Acute Cardiac Humoral Rejection: A Case Report,” Transplantation, Vol. 73, 907-910, No. 6, March 27, 2002, describe the successful use of rituximab in the treatment of a 50 year

old woman who underwent heart transplantation in March 2000. The patient experienced significant humoral rejection resistant to steroids, cyclophosphamide and plasmapheresis, but responded favorably to the administration of rituximab. On postoperative day 21, due to ongoing humoral rejection, rituximab was given at a dose of 375 mg/m² infusion weekly for 4 weeks in addition to plasmapheresis, OKT3 and cyclophosphamide therapy. Applicant notes that this regimen is generally described at page 41 of the specification of the instant application, and is specifically described in Example 3 of the patent. Applicants further note that *Aranda et al.* conclude that “rituximab constitutes the first B cell-specific therapy available to transplant clinicians.”

The Examiner is invited to specifically review *Aranda et al.*, including, in particular, the treatment modalities employed, the specific findings regarding the patient’s progression, and other observations made therein.

Applicants also submit that the concern expressed by the Examiner over the nature of Example 3 (e.g., that it is a “prophetic” example; see, e.g., page 4, second paragraph, page 6, last paragraph) are not an appropriate basis for imposing a rejection under 35 U.S.C. 112, first paragraph. This is particularly so in view of the evidence submitted herewith showing results from the use of the claimed invention according to the teachings in the specification, including, in particular, Example 3.

Accordingly, Applicants submit that the hypothetical concerns set forth in the last Office Action are not an appropriate basis for asserting that the claimed invention is not enabled by reason of lack of a credible utility, particularly in view of the evidence submitted herewith. Where an applicant provides a sufficient basis, in the application as filed and through additional evidence, that a claimed invention yields the desired results, a rejection

under 35 U.S.C. 101, or a rejection under 35 U.S.C. 112, first paragraph, based on the theory that the invention is inoperable, is inappropriate. See, generally, M.P.E.P. 2107, *et seq.* Such a basis is evident both from the present specification, and from the additional evidence in the form of publications provided herewith.

(ii). Undue Experimentation Grounds

In addition to issues concerning the credibility of the utility asserted for the presently claimed invention, the Examiner has set forth a number of observations suggesting that the practice of the claimed invention, relative to the instant application, would require undue experimentation from a person of ordinary skill in the art. In particular, the Examiner urges that

- (a) the specification is not enabled for any route of administering an antibody that binds to CD20 into a mammal because it offers no guidance on how to achieve the desired results via intravenous delivery of rituximab, let alone any route of delivery such as oral, subcutaneous or mucosal delivery; and
- (b) the specification fails to provide sufficient guidance for a skilled artisan to make and use any anti-CD20 polyclonal antibody possessing the same biological activities as those of rituximab to attain the therapeutic effects contemplated by Applicants for the claimed methods.

Applicants respectfully disagree with the characterizations of the instant disclosure made by the Examiner, and believe the disclosure provides more than ample guidance to a person of skill in the relevant art to practice the invention as it is claimed.

First, Applicants submit that a person of ordinary skill in this art is able to determine appropriate modalities for administration of anti-CD20 antibodies using the teachings of the present specification. For example, appropriate pharmaceutical formulations are described in extensive detail at pages 38 to 40 of the specification, with references to publications providing further information on such formulations. Treatment modalities are described in

depth at pages 40 to 44, with specific exemplification of the presently claimed method at pages 46 to 47.

In addition, in response to the specific assertion of the Examiner at page 7 that the present application does not adequately teach how to achieve the desired results via intravenous administration, the Examiner's attention is directed to page 41, lines 21-23 of the specification, where it is disclosed that a therapeutically effective dosage for parenteral administration per dose in the range of about 0.1 to 20 mg/kg of patient body weight. As set forth at page 42, lines 3-8, the antibody may be administered in one or more subsequent doses. At page 41, lines 10-15 it is disclosed that the key factor in selecting an appropriate dose and scheduling is the result obtained. For example, relatively higher doses may be needed initially for the treatment of ongoing and acute diseases. To obtain the most efficacious results, depending on the disease or condition, the antagonist is administered as close to the first sign, diagnosis, appearance, or occurrence of the disease or condition as possible or during remissions of the disease or condition. At page 41, lines 16-20, the instant specification provides that:

[A] composition comprising an antagonist which binds to CD20 will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disease or condition being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disease or condition, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

In addition, as set forth above, in both published studies of rituximab therapy, administration was by weekly infusion of rituximab, 375 mg/m² for 4 weeks, consistent with the treatment regimen as set forth in Example 3 of the specification.

In view of the above, the specification clearly provides sufficient guidance on how to achieve the desired results via intravenous delivery of the claimed anti-CD20 antibody as well as by other routes of delivery. The Examiner is respectfully requested to withdraw the rejection of the claims on this basis.

The Examiner further urges that the specification does not enable the use of anti-CD20 antibodies of the breadth specified in the claim. At page 8, the examiner raises specific questions regarding polyclonal antibodies, non-human antibodies that lack human effector functionality, and antibodies that would be recognized as foreign by the human and would thus be neutralized before they reach their target site.

Applicants respectfully submit that the specification is fully enabling for the scope of the claims presented. In particular, the present specification describes in extensive detail both the theory of the claimed process (see, e.g., page 4, line 27 to page 5, line 8), and specific embodiments of anti-CD20 antibodies that may be used in that process (see., e.g., page 8, line 24, to page 16, line 7). The structural and functional attributes of the anti-CD20 antibodies that may be used in the claimed process are clearly exemplified in the specification, and would not require undue experimentation, based on the instant disclosure, to prepare and use according to the claimed method. Applicants respectfully submit that a person of ordinary skill would not have to resort to undue experimentation to either select an appropriate anti-CD20 antibody within the meaning of the claims for use in the claimed method, or to use and administer such agent pursuant to the claimed method when the teachings of the instant specification are considered.

Accordingly, Applicants respectfully request the Examiner to withdraw the rejections of claims 1, 5 to 16, 22 and 28 under 35 U.S.C. 112, first paragraph.

Rejection of Claim 13 Under §112, Second Paragraph

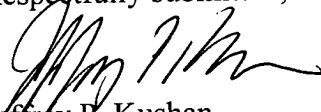
Amended claim 13 is rejected under §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons already set forth in the previous Office Action. The Examiner maintains that “a dose substantially less than 375 mg/m² in claims 13 is a relative term which renders the claim indefinite. The Examiner has taken the position that the metes and bounds of the claim are not clearly determined on the basis that the lower limit of a dose is not clearly defined .

Applicants have amended claim 13 to specify a lower and upper limit for the amount of antibody to be administered. Support for this amendment may be found in the specification at page 41, lines 26-27. Applicants respectfully request the Examiner to withdraw the rejection of claim 13 in view of this amendment.

CONCLUSION

In light of the above amendments and remarks, applicants respectfully submit that all pending claims as currently presented are in condition for allowance. If, for any reason, the Examiner disagrees, please call the undersigned attorney at 202-736-8914 so that Applicant may attempt to resolve any matter still outstanding *before* issuing another action. Favorable reconsideration is respectfully requested.

Respectfully submitted,



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